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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,757	06/04/2001	Nnochiri N. Ekwuribe	9233-62	2357

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EXAMINER
RUSSEL, JEFFREY E

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,757	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *October 10, 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The disclosure is objected to because of the following informalities: At page 10, line 22, "serine" is misspelled. Appropriate correction is required.

2. The drawings are objected to because in the y-axis label of Figures 29 and 30, "luciferase" is misspelled. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

3. The abstract of the disclosure is objected to because it is insufficiently detailed with respect to the characteristics of the conjugates and the polyalkylene glycol moieties (i.e. their molecular weight distribution, uniformity, monodispersity, etc.) and with respect to the uses of the conjugates. Correction is required. See MPEP § 608.01(b).

4. Claims 4, 5, 31, 32, 34, 37, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4, 5, 31, 32, 34, and 37 are indefinite because it is not clear what are the lower limits to the ranges specified in the claims. For example, with respect to claim 4, assuming that "at least 2" is the lower limit to the number of PEG subunits, it is at best redundant to state that greater numbers of PEG subunits may be present. Assuming that 3 or 4 is intended to be the lower limit to the claimed ranges, then it is contradictory to also recite "at least 2". Claims 5, 31, 32, 34, and 37 are indefinite for analogous reasons. There is no antecedent

basis in the claims for the phrase "the polypropylene glycol moiety" at claim 47, line 1. It is believed that claim 47 should instead depend upon claim 46.

5. Claims 39 and 54-57 are objected to because of the following informalities: At claim 39, line 2, "glycol" should be inserted after "polypropylene" so that the claim terminology is consistent with that at line 1. At claim 54, page 110, line 12, the semicolon after "moiety" should be changed to a comma, and the comma after "m is 1" should be changed to a semicolon. Appropriate correction is required.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-103 of copending Application No. 09/873,797. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '797 application anticipate instant claims 1-8, 13-27, and 30-67. Note that the '797 application claims purely monodispersed mixtures of a drug coupled to a polyalkylene glycol moiety (see, e.g., claim 1) where the drug can be growth hormone peptides (see, e.g., claim 64) and the polyalkylene glycol moiety can be polyethylene glycol or polypropylene glycol (see, e.g., claims 21 and 23), and that the '797

application claims forming these conjugates (see, e.g., claims 95-102) by the same method claimed in the instant application. With respect to claims 9-12, while the '797 application does not claim human growth hormone as a source of the growth hormone to be conjugated, it would have been obvious to one of ordinary skill in the art to use human growth hormone as the source of the growth hormone in the claimed invention of the '797 application because human growth hormone is a known source of therapeutic growth hormone, and because conjugation of human growth hormone according to the claimed invention of the '797 application would have been expected to increase the human growth hormone's resistance to in vivo proteolysis and to increase its in vivo have-life. With respect to claims 28 and 29, while the '797 application does not claim the use of its growth hormone conjugates to treat growth hormone deficiency or to accelerate the growth rate of an animal, it would have been obvious to one of ordinary skill in the art to use the growth hormone conjugates of the '797 application to treat growth hormone deficiency or to accelerate the growth rate of an animal, because these are common uses for growth hormone and because it is routine to use conjugated protein or peptide therapeutics to treat diseases which are known in the art to be treatable with the unconjugated protein or peptide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 59-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of copending Application No. 09/873,731 in view of Clark (U.S. Patent No. 5,597,797) or Cunningham et al (U.S. Patent No. 6,057,292). Although the conflicting claims are not identical, they are not patentably distinct from each other. The '731 application claims the same method steps as are

recited in the instant claims for forming the substantially monodispersed mixture of polymers having the structure of Formula III, but does not claim then activating the polymers and reacting them with growth hormone in order to form growth hormone conjugates. Clark teaches forming PEG-human growth hormone conjugates by first activating the PEG and then reacting the activated PEG with the human growth hormone, preferably with the epsilon-amino group of a lysine residue (see, e.g., column 5, lines 45-57; column 10, lines 50-56; and column 13, lines 34-39). Cunningham et al teach forming PEG-human growth hormone conjugates by first activating the PEG and then reacting the activated PEG with the human growth hormone, preferably with the epsilon-amino group of a lysine residue (see, e.g., column 20, line 53 - column 21, line 67; column 23, lines 45-55; and column 25, lines 11-39). It would have been obvious to one of ordinary skill in the art to use the claimed method of the '731 application as a source of the PEG used in Clark's method or Cunningham et al's method for forming PEG-human growth hormone conjugates because it is prima facie obvious to use the product of one process as the source of reactant for another process (see In re Kamlet, 88 USPQ 106 (CCPA 1950)).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

10. Claims 1-6, 9-12, 16, 18, 22, 23, 26, 27, 30-38, 42-45, 48-50, and 53 are rejected under 35 U.S.C. 103(a) as being obvious over Clark (U.S. Patent No. 5,597,797) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Clark teaches preferably 2-8 polyethylene glycol molecules having a molecular weight of 5,000 - 40,000 preferably conjugated to epsilon-amino groups of lysine residues present in human growth hormone. See, e.g., column 5, lines 45-57; column 10, lines 11-56; and column 13, lines 34-39. Clark does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page

2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-growth hormone conjugates of Clark using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Clark; because the use of discrete length PEG in the conjugates of Clark would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

11. Claims 1-6, 9-12, 16, 18, 22, 23, 26-38, 42-45, 48-50, and 53 are rejected under 35 U.S.C. 103(a) as being obvious over Cunningham et al (U.S. Patent No. 6,057,292) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Cunningham et al teach preferably about 4-6 polyethylene glycol molecules having a molecular weight of 4,000 - 20,000 preferably conjugated to epsilon-amino groups of lysine residues present in human growth hormone The conjugates are used, e.g., to treat growth hormone deficiency and to accelerate growth of humans. See, e.g., column 20, line 53 - column 21, line 54; column 23, lines 45-55; column 25, lines 11-39; and column 27, lines 2-20. Cunningham et al do not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of

optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-growth hormone conjugates of Cunningham et al using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Cunningham et al; because the use of discrete length PEG in the conjugates of Cunningham et al would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

12. Claims 1-6, 16-23, 26-38, 42-44, 48, 49, 53, 54, and 58 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Ekwuribe teaches conjugates in which a polymer comprising a PEG moiety which preferably has more than 7 subunits and a lipophilic moiety is conjugated via a labile bond to a peptide, which can be

somatotropin (i.e. growth hormone) and which conjugation can occur at an amine group present on the peptide Plural polymers can be conjugated to each peptide. Conjugation results in prolonged blood circulation and enhanced resistance to enzymatic degradation, relative to the peptide alone. See, e.g., the Abstract; column 6, lines 41-61; column 11, line 20; column 12, lines 11-16 and 35-40; column 13, Conjugates 2 and 3; and column 14, lines 3-14 and 43-55. While Ekwuribe does not teach using somatotropin-based conjugates to treat growth hormone deficiency or to accelerate the growth rate of an animal, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the somatotropin-based conjugates of Ekwuribe for these purposes because the treatment of growth hormone deficiency and the acceleration or growth rate are primary uses of somatotropin. Ekwuribe does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application 97/14740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the somatotropin conjugates of Ekwuribe using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88

USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Ekwuribe; because the use of discrete length PEG in the conjugates of Ekwuribe would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

13. Claims 9-12, 28, 29, 45, and 50 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 1-6, 16-23, 26-38, 42-44, 48, 49, 53, 54, and 58 above, and further in view of the Harris et al article (J. Macromol., Sci., Vol. C25, pages 325-373), Clark (U.S. Patent No. 5,597,797), or Cunningham et al (U.S. Patent No. 6,057,292). Ekwuribe does not teach the number or the size of the oligomers which are to be conjugated to each somatotropin molecule. The Harris et al article teaches that when using PEG-protein conjugates, the degree of substitution and PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, as taught by the Harris et al article for the PEG-somatotropin conjugates of Ekwuribe in order to maximize the conjugates' desirable properties. Ekwuribe does not teach using somatotropin-based conjugates to treat growth hormone deficiency or to accelerate the growth of animals. Cunningham et al teach polyethylene glycol conjugated to human growth

hormone and used to treat growth hormone deficiency and to accelerate the growth of animals. See, e.g., column 20, line 53 - column 21, line 54; column 23, lines 45-55; column 25, lines 11-39; and column 27, lines 2-20. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the somatotropin-based conjugates of Ekwuribe for the above-recited purposes because the treatment of growth hormone deficiency and the acceleration of the growth rate of animals are primary uses of somatotropin conjugates as shown by Cunningham et al. Ekwuribe does not teach using human somatotropin as the source of the somatotropin for its conjugates, and does not teach conjugation at the amino groups present in the human somatotropin. Clark teaches conjugating polyethylene glycol molecules preferably to epsilon-amino groups of lysine residues present in human growth hormone. See, e.g., column 5, lines 45-57; column 10, lines 11-56; and column 13, lines 34-39. Cunningham et al teach conjugating polyethylene glycol molecules to epsilon-amino groups of lysine residues present in human growth hormone. See, e.g., column 20, line 53 - column 21, line 54; column 23, lines 45-55; column 25, lines 11-39; and column 27, lines 2-20. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use human somatotropin as the source of the somatotropin for the conjugates of Ekwuribe because Clark and Cunningham et al et al teach that human growth hormone is an effective source of somatotropin in making such conjugates and because human somatotropin possesses therapeutic properties which would have been expected to have been useful in the conjugates of Ekwuribe. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to conjugate the polymers of Ekwuribe to the sidechains of the Lys residues present in human somatotropin because Clark and Cunningham et al disclose that these residues are useful attachment points for

forming somatotropin conjugates.

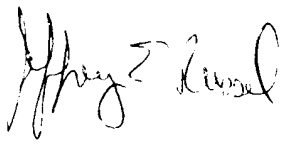
14. Instant claims 24 and 25 are not rejected over the prior art applied above, because the prior art of record does not teach or suggest the claimed oligomer structure in which one polyalkylene glycol moiety is covalently coupled to another through a hydrolyzable bond.

Instant claims 7, 8, 13-15, 39-41, 46, 47, 51, 52, and 55-57, which require the presence of polypropylene glycol moieties in the oligomer, are not rejected over the prior art applied above, and in particular over Delgado et al (U.S. Patent No. 5,349,052) or the WO Patent Application 97/14740, because this prior art does not teach or suggest how to make polypropylene glycol which satisfies Applicants' claimed molecular weight distribution or dispersity limitations. The disclosures of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 are limited to polyethylene glycol, and their syntheses and purifications do not necessarily extrapolate to polypropylene glycol.

The Coudert et al article (Synth. Comm., Vol. 16, pages 19-26) is deemed to be the closest prior art of record with respect to instant claims 59-67. However, the Coudert et al article does not teach or suggest the use of a mesylate activating group in reacting its ethylene glycol subunits with one another (see page 20).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

February 13, 2003